

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA

### I. GENERAL INFORMATION

Device Generic Name: Human papillomavirus DNA detection kit

Device Trade Name: Digene Hybrid Capture 2 High-Risk HPV DNA Test

Applicant's Name and Address: Digene Corporation  
1201 Clopper Road  
Gaithersburg, Maryland 20878

Date of Panel Recommendation: March 8, 2002

Premarket Approval Application (PMA) Number: P890064/S009

Date of Notice of Approval to Applicant: March 31, 2003

### II. BACKGROUND

The device was originally approved on March 11, 1991. A subsequent PMA supplement (P890064/S007) was approved on March 16, 2000, which included a revision to the indication for use as follows:

1. To screen patients with ASCUS (atypical squamous cells of undetermined significance) Pap smear results to determine the need for referral to colposcopy. The results of this test are not intended to deter women from proceeding to colposcopy.
2. In women with LSIL or HSIL Pap smear results, prior to colposcopy, an HCII HPV result will aid the physician in patient management by assisting with risk assessment of women to determine absence of high-grade disease. This result is not intended to deter the patient from proceeding to colposcopy.

The applicant submitted the current supplement (P890064/S009) to further expand the indications for use. The updated clinical data to support the expanded indication is provided in this summary.

### III. INDICATIONS FOR USE

The Digene Hybrid Capture 2 High-Risk HPV DNA Test (hereinafter called the Digene hc2 High-Risk HPV Test) indication for use #2 above has been replaced with the following:

2. In women 30 years and older, the hc2 High-Risk HPV DNA Test can be used with

Pap to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician's assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.

#### IV. CONTRAINDICATIONS

None known

#### V. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Digene hc2 High-Risk HPV Test labeling.

#### VI. DEVICE DESCRIPTION

The Digene hc2 High-Risk HPV Test is a nucleic acid hybridization assay with signal amplification that utilizes microplate chemiluminescent detection. Specimens containing the target DNA hybridize with a specific HPV RNA probe cocktail. The resultant RNA:DNA hybrids are captured on to the surface of a microplate well coated with antibodies specific for RNA:DNA hybrids. Immobilized hybrids are then reacted with alkaline phosphatase conjugated antibodies specific for the RNA:DNA hybrids, and detected with a chemiluminescent substrate. Several alkaline phosphatase molecules are conjugated to each antibody. Multiple conjugated antibodies bind to each captured hybrid resulting in substantial signal amplification. As the substrate is cleaved by the bound alkaline phosphatase, light is emitted which is measured as relative light units (RLUs) on a luminometer. The intensity of the light emitted denotes the presence or absence of target DNA in the specimen.

An RLU measurement equal to or greater than the Cutoff Value indicates the presence of high-risk HPV DNA sequences in the specimen. An RLU measurement less than the cutoff value indicates the absence of the specific high-risk HPV DNA sequences test or HPV DNA levels below the detection limit of the assay.

#### VII. MARKETING HISTORY

The Digene hc2 High-Risk HPV Test is marketed in the European Union (including Switzerland), Canada, Brazil, and the U.S.

The Digene hc2 High-Risk HPV Test has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

#### VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

As an *in vitro* diagnostic test system, there is no direct adverse effect of the Digene hc2 High-Risk HPV Test on the health of the patient. The possibility of erroneous test results due to test malfunctions or operator error exists.

A false positive test may be of concern to patients because it would indicate that the patient had acquired a sexually transmitted disease, and would erroneously assign a risk factor for development of cervical cancer to the patient. Consequently, the patient might suffer psychosocial difficulties and change in family dynamics related to the conditions of acquisition of the virus, and might be unnecessarily treated using invasive and uncomfortable procedures.

A false negative test would have different consequences depending on the Pap result for which the adjunctive HPV test was sought. A woman with a normal Pap result and a false negative HPV result would not be alerted to the presence of a risk factor and might delay future cervical cancer screenings believing that she was at very low risk. A woman with an ASCUS Pap result and a false negative HPV result might not be referred to appropriate treatment in a timely manner.

There are additional concerns about adverse effects of HPV infection status that are associated with true positive results, when Pap results are normal. First, although some data exists to suggest increased risk for development of CIN 2-3 and cancer when HPV is present in women with normal Pap results, the increase in absolute risk is probably small. To date, no adequate longitudinal study has been published that specifically addresses the risk of CIN 2-3 or cancer in Pap normal women with and without HPV infection. Second, currently there is no treatment customarily offered for HPV infection when Pap results are normal, so a positive result adds psychosocial anxiety without offering treatment options. Finally, most women who acquire an HPV infection clear the infection without developing any symptoms or cervical cell abnormalities. Knowledge of a positive HPV result for these women might only serve to create unwarranted distress.

The psychosocial risks of the results of HPV testing would primarily be mitigated by appropriate patient and physician counseling and free availability of information about what HPV results mean in the context of cervical cancer screening. Counseling and other information are expected to be provided to and by the clinical community in the form of direct patient counseling and brochures discussing HPV testing directed at physicians and patients. The American Cancer Society has developed a brochure that is freely available on the web at [http://www.cancer.org/docroot/NWS/content/NWS\\_2\\_1x\\_What\\_Women\\_Should\\_Know\\_about\\_HPV\\_and\\_Cervical\\_Health.asp](http://www.cancer.org/docroot/NWS/content/NWS_2_1x_What_Women_Should_Know_about_HPV_and_Cervical_Health.asp). Another group consisting of experts in the field has created a physician's guideline explaining when to use, and how to interpret the results of the test in women over thirty. This guideline is expected to be published in a peer-reviewed journal within the year.

## IX. SUMMARY OF PRECLINICAL STUDIES

Preclinical studies were presented by Digene in a previously approved PMA supplement (P890064/S006). No additional laboratory testing was done in support of this supplement because no changes were made to the previously approved Digene hc2 High-

## Risk HPV Test.

### Analytical Sensitivity

A nonclinical panel of cloned HPV plasmid DNA was tested to determine if each of the 13 HPV types are detectable by the hc2 High-Risk HPV Test and to determine the analytical sensitivity of the assay for each of the HPV types. Each HPV target concentration (100 pg/ml, 10 pg/ml, 2.5 pg/ml, 1.0 pg/ml, 0.5 pg/ml, and 0.2 pg/ml) of each of the 13 HPV DNA types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) was run in triplicate. The mean signal (in RLUs) for each concentration of each HPV type was calculated and compared to the positive cut-off value (HRCx). The detectable limits varied from 0.62 pg/ml to 1.39 pg/ml depending on the HPV type tested (from P890064/S006). The mean detectable limit of all 13 HPV DNA types was 1.08 pg/ml of HPV DNA with a standard deviation of 0.05 pg/ml.

### Reproducibility

A multicenter reproducibility study was performed to determine the between days, between sites, and overall reproducibility of the Digene hc2 High-Risk HPV Test using a panel of HPV DNA targets and HPV-positive and HPV-negative clinical specimens.

Three external laboratories performed the testing with the same lot of Digene hc2 High-Risk HPV Test kits on three different days with an identical reproducibility panel. The reproducibility panel included the following specimens: 12 denatured clinical STM specimen pools; three undenatured clinical PreservCyt Solution specimen pools; Negative Control; and Positive High-Risk HPV Calibrator at concentrations of 1 pg/ml, 0.5 pg/ml, 2.5 pg/ml, 5 pg/ml and 10 pg/ml. All panel members were tested each day in triplicate. The results are included in P890064/S006 and showed satisfactory results for these type studies.

Cross-Reactivity and Interference studies were also presented in P890064/S006 which showed satisfactory results for these type studies.

## X. SUMMARY OF CLINICAL STUDIES

Digene submitted data from two longitudinal studies carried out in Portland, Oregon, USA and in Reims, France, to support their expanded indications for use. Sufficient data from these studies were not readily available to support Digene's proposed claim. It was determined that sufficient peer-reviewed literature existed to establish an amended set of claims, for which the data from the submitted studies were not needed in order to establish that the device was reasonably safe and effective for the expanded indications (see section III).

### Test Performance in Clinical Samples in Women 30 Years and Older

Although no clinical trial was performed specifically to support the use of the Digene hc2 High-Risk HPV Test as an adjunct to the Pap test, compared with Pap test alone,

consistent data obtained from multiple cross-sectional and prospective cohort studies conducted with a variety of cell sampling methods and utilizing the Digene hc2 HPV Tests and several research-use testing methods provide evidence that a negative HPV DNA test implies low risk of prevalent or incipient CIN 2-3 or cancer when Pap results are within normal limits (WNL) (Ref: 1-27).

The new claim for testing of women 30 years and older without specific Pap test results was approved based on consistent published data obtained from multiple cross-sectional and prospective cohort studies conducted with a variety of cell sampling and HPV testing methods, including the Digene hc2 High-Risk HPV Test (Ref: 1-27). These data provide reasonable evidence that a negative HPV DNA test implies very low risk of prevalent or incipient CIN 2-3 or cancer when Pap results are WNL.

Digene, in consultation with FDA, elected to remove the previously approved claim for use of HPV testing in women with LSIL or HSIL Pap results:

“In women with LSIL or HSIL Pap smear results, prior to colposcopy, a Digene hc2 High Risk HPV DNA Test result will aid the physician in patient management by assisting with risk assessment of women to determine absence of high-grade disease. This result is not intended to deter the patient proceeding to colposcopy.”

Additional studies have established that LSIL is essentially the cellular manifestation of HPV infection, and that women with HSIL results almost always have HPV infection, and should be followed up regardless of HPV infection status. Thus, there is no utility for HPV testing in women with LSIL or HSIL Pap results.

## XI. CONCLUSIONS DRAWN FROM THE STUDIES

Review of the published literature articles submitted for consideration in assessing the new claims in this submission supported the following conclusions relevant to the new intended use, in which application of the Digene hc2 High-Risk HPV Test to women with normal Pap results is approved:

1. There is a variable rate of HPV infection that can be detected in women who have Pap test results that are WNL.
2. HPV prevalence for women under 30 years of age is high, and most infections resolve. HPV prevalence for women 30 years of age and older is lower, and is more frequently associated with underlying CIN 2-3 and cancer. The “false positive” rate of HPV testing for underlying CIN 2-3 or cancer is not acceptable for women under 30 years of age.
3. Women 30 years of age and older who are HPV negative and have WNL Pap test results have a very low risk of developing CIN within one year to 18 months, i.e., the combined test result has a high negative predictive value when Pap is WNL and HPV is negative.
4. Persistent HPV infection is a significant risk factor for development of CIN 2-3 and cancer.

5. A large proportion, but not all, of CIN 3 is associated with high-risk HPV infection. The proportion varies among different studies.
6. No longitudinal literature exists at this date that reliably establishes a low risk status equivalent to consecutive WNL Pap test results

Therefore, it is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use. See "References" section for references that were used in order to come to this determination.

## SAFETY

The safety of the Digene hc2 High-Risk HPV Test is acceptable, as it is used adjunctively, and on an *in vitro* basis. No clinical assessment or treatment decisions should be made based on the results of the Digene hc2 High-Risk HPV Test alone.

## EFFECTIVENESS

The effectiveness of the Digene hc2 High-Risk HPV Test has been previously demonstrated for use in assessing high risk HPV infection, and for using the Digene High-Risk HPV Test results in conjunction with ASCUS Pap results. A reasonable determination of effectiveness of the Digene hc2 High-Risk HPV Test for aiding in clinical management of women with WNL Pap results has been drawn from multiple cross-sectional studies that included women with WNL Pap results and who were either HPV DNA-positive or -negative (Ref: 1-27). These studies indicate that women who are HPV DNA-negative have a very low risk of underlying or incipient CIN 2-3 or cervical cancer.

## XII. PANEL RECOMMENDATION

At an advisory meeting held on March 8, 2002, the Microbiology Devices Advisory Panel recommended that Digene's PMA supplement for the Digene hc2 High-Risk HPV Test be approved subject to the following conditions:

- (1) The sponsor should provide specific recommendations for how to use the test in clinical management (including how to interpret results near the cut-off)
- (2) The sponsor must demonstrate that the recommendations will have a positive impact on clinical outcomes. These conditions could be satisfied by evidence based on data derived from longitudinal studies.

- (3) The sponsor must develop educational materials to accompany the tests both for laboratory users and clinicians.
- (4) Post approval study must be conducted to assess the impact of the device performance on clinical outcomes.

### XIII. CDRH DECISION

CDRH concurred with the Microbiology Advisory Panel's recommendation for conditions for approval of March 8, 2002, but found that the conditions were consistent with a non-approvable decision. CDRH issued a letter to Digene, on March 26, 2002, advising Digene that its PMA supplement was not approvable. CDRH stated that the submission could be placed in approvable form subject to Digene's provision of the items recommended by the Panel and required by FDA as follows:

- (1) Additional data and analyses to support a diagnostic algorithm for the use of this device for the expanded indication for use. These data should also demonstrate that the information generated for the general high-risk HPV screening in conjunction with the Papanicolaou smear will provide clinically significant results in the target population.
- (2) An educational program that communicates the proposed diagnostic algorithm, with information on test use and interpretation, for both clinicians and patients.
- (3) A post approval study plan designed to confirm the device's stated performance in the U.S. population and measures the impact of the proposed high-risk HPV testing on screening program outcomes.

In an amendment received by FDA on September 30, 2002, Digene submitted data, including study results, published literature and information supporting Digene claims, proposed post approval activities (post approval study plan, patient and physician education materials), and revised labeling. FDA determined that the least burdensome way to address the educational program recommended by the panel was to reference patient materials and physician guidelines developed through a committee of experts in the field and funded by the National Institutes of Health-National Cancer Institute, the American Society of Colposcopy and Cervical Pathology, and the American Cancer Society. FDA also determined that a post approval study plan was not necessary since the final labeling was revised to incorporate the final set of claims based on published literature.

The applicant's manufacturing facility was inspected on May 23, 2001, and was found to be in compliance with the device Quality Systems Regulations.

FDA issued an approval order on March 31, 2003.

#### XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.

#### XV

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